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Uremic memory: the role of acute kidney injury in long-term outcomes

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Most epidemiologic data, thus far, have focused on short-term outcomes of acute kidney injury (AKI). Lo *et al.* correlate AKI with long-term outcomes. The concept of 'uremic memory' sheds light on the importance of AKI and its permanent imprint. The focus of research should be on prevention of an episode of AKI, when possible.

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In the short term, acute kidney injury (AKI) leads to death. Population-based studies have identified in-hospital case-fatality rates for AKI, variously defined, ranging between 45% and 70%.[1] In 2005, Chertow *et al.* analyzed data from nearly 20,000 consecutive admissions to an urban medical center and found that an increase of creatinine as small as 0.3 mg/dl conferred a 70% increase in adjusted odds of death.[2] The RIFLE criteria, first introduced as a means to standardize definitions of AKI and target research and care, have become a risk stratification tool for in-hospital mortality. With increasing degrees of renal dysfunction, regardless of renal outcome, mortality increases in a graded and faithful manner.[3]

The epidemiologic link is solid between AKI and short-term morbidity and mortality. Long-term implications of an episode of AKI have been less well explored. Early studies estimating long-term risk after an episode of AKI consisted of small prospective observational studies of incident patients with AKI. They consistently found a decrease in glomerular filtration rate (GFR) months after the initial insult,[4,5] even with full restoration of renal blood flow. The reduction in GFR was seldom less than 50 cc/min from baselines of about 100 ml/min and was therefore ignored, and the effect on long-term mortality was frequently underestimated. Residual chronic kidney disease (CKD) was attributed to obliteration of nephrons with the AKI episode.[6] Other early histologic changes included vascular denudation, patchy scarring, and dilated tubules with flattened epithelium.[4] The consistent long-term decrease in creatinine clearance does argue for a structural lesion involving the nephrons in all cases (Figure 1).

Recent epidemiology reveals that an episode of AKI, regardless of recovery and extent of recovery, unequivocally leads to increased mortality and increased CKD, in the long term.[1,7,8] The more severe the episode of AKI, the more robust is this correlation. The etiology of AKI and its duration do not seem to contribute to this correlation.[1,7] While mild AKI is associated with a 70% increase in mortality risk, the risk of long-term death was nearly threefold greater in patients with mild to moderate AKI as compared with their non-AKI counterparts.[7] In an attempt to survey the chronic consequences of AKI, the National Institute of Diabetes and Digestive and Kidney Diseases has funded a prospective study composed of a consortium of several institutions, AKI-ASSESS. The results of their work are several years away.

Although critiques of the causal role of AKI in short- and long-term mortality argue that those patients who get AKI are simply sicker, there is enough evidence to suggest that, independent of confounding variables, AKI causes some bad outcomes. The pathophysiology of AKI and its effects on remote organs are topics of great interest that have been most extensively researched in animal models. Chemical mediators (such as cytokines, complement, chemokines, and oxygen free radicals) play a large role in the inflammatory response of AKI.[9] Ischemia and hypoxia as direct insults to the tubulointerstitial cells initiate transcription of proinflammatory cytokines (such as interleukin-1, interleukin-6, and tumor necrosis factor-α).[9] These mediate the cascade of inflammatory reactions, furthering injury during the reperfusion phase. These systemic events affect distant organs as well. Cardiac alterations, abnormal lung physiology, and endothelial dysfunction have all been implicated during AKI.[9]

Animal studies examining long-term effects of AKI have demonstrated structural and functional residua to experimental AKI. In a rat model, an episode of ischemia/reperfusion (I/R) was shown to have long-term effects on renal function despite complete clinical recovery.[10,11] Morphologic studies showed that impaired function was associated with widespread tubulointerstitial disease. Some tubules were atrophic and others dilated. The interstitial volume fractions were increased. Furthermore, while many glomeruli retained open capillary loops after injury, they were disconnected from their respective tubules after I/R injury.[10] In fact, GFR was closely related to the number of glomeruli that remained connected to normal tubules. In addition, single-nephron GFR values returned to normal after I/R, but there was complete loss of function in a large portion of the nephrons.[10] Mouse models show vascular rarefaction, increased interstitial fibrosis, and dilated tubules long after one episode of I/R, despite complete clinical recovery.[11]

Lo *et al.*[12] (this issue) now rigorously examine the long-term sequelae of AKI. Theirs is a retrospective analysis of the large Kaiser Permanente database using the years 1996–2003. They explore AKI and its correlation with long-term kidney disease and mortality in comparison with enrollees of the same health-care organization who did not develop AKI and thus served as controls. Their study focuses on

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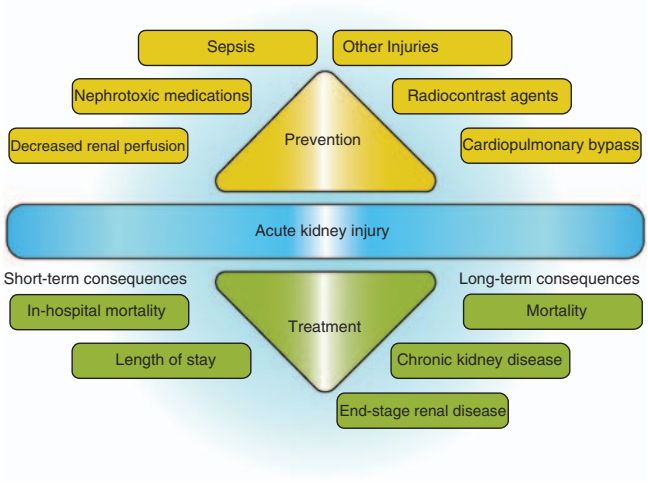

Figure 1 | Epidemiologic associations between causes and consequences of acute kidney injury and potential areas where physicians can effect change in these associations.

patients with estimated GFRs greater than 45 cc/min/1.73 m^2 at baseline. As compared with controls, patients who suffered dialysis-dependent AKI during their hospitalization had a 28-fold increased risk of developing stage 4 CKD or end-stage renal disease. There was also a more than two-fold risk of long-term death in this group. Although the major differences between cohorts in their baseline characteristics is a source of bias, at the very least, AKI serves as an easily assessable prognostic marker for long-term CKD and long-term morality. Matching of the cohorts was used to reduce some of this bias, as were multivariate and sensitivity analyses. Thus the internal validity of AKI and its causal role in CKD and mortality, within the limits of statistical ability, is established.

The distinction between structural (parenchymal) renal damage and functional renal disease during an episode of AKI is practically impossible. Serum markers such as urea and creatinine are incapable of making this distinction, and newer urinary biomarkers have so far fallen short of doing so. At what point does decreased renal perfusion, which implies vascular pathology only, with an element of reversibility, become irreversible and definitive in its parenchymal insult to the tubules? Certainly one would expect that the greater the degree of damage to the parenchyma of the kidney, the worse the consequences. Perhaps the dramatic surge of mediators and immune factors occurs in response to any alteration in the normal kidney milieu. The kidney, because of its intense metabolic and oxygen requirements, is particularly sensitive, and by the time an increase in creatinine (still the gold-standard marker for any of the new definitions) occurs, a great deal of damage with long-term consequences has occurred.

An episode of hyperglycemia causes dramatic changes in gene expression of nuclear factor-κB, monocyte chemoattractant protein, and vascular adhesion molecules.[13] This effect, known as hyperglycemic memory, highlights the dramatic and long-lasting effects that short-term hyperglycemic spikes may have on vascular beds and suggests a mechanism for long-term sequelae. We believe an analogous model might explain the long-term effects of an episode of AKI. 'Uremic memory' consists of permanent pathologic changes visited on the kidney with an episode of AKI. Interstitial fibrosis, vascular denudation and degradation, atubular glomeruli, and a higher interstitial-to-glomerular ratio are some histologic imprints of a past episode of AKI.[10,11] The upsurge of profibrotic and apoptotic factors after an acute episode of inflammation and the effects on remote organs is further evidence to support the concept of uremic memory.[9]

AKI causes CKD and death in both the short and the long term. Uremic memory enables one episode of AKI, regardless of complete recovery, to leave an imprint in a patient, putting him or her at risk for long-term morbidity and mortality. Treatments to hasten recovery of established AKI remain elusive, but even if such a treatment became available, this residue of damage might persist with chronic decay in renal function. Prevention would seem a very important focus of AKI research. After all, much AKI occurs as a result of what happens to a patient once in the medical system and, if not strictly iatrogenic, is at least potentially avoidable or mitigable. Perhaps we should risk-stratify all patients who are hospitalized for AKI risk, or at least those who are expected to undergo certain procedures. We need to devise methods by which we can prevent AKI in the setting of a known renal insult, such as contrast, cardiopulmonary bypass, vascular intervention, or nephrotoxic medication. Any degree of prevention is worthy of consideration, as even subtle derangements in the kidney can have both short- and long-term consequences.

DISCLOSURE

The authors declared no competing interests.

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